

Thermosensors or thermostats: new arguments

Shigeo Kobayashi*

Graduate School of Informatics; Kyoto University; Sakyo-Ku, Kyoto, Japan

Dear Editor-in-Chief:

This is my reply to the letters^{1–6} written in response to my recent article.⁷

Dr. Flouris¹ appears to support my article.⁷ However, I refute some of the comments made by Flouris.

Reply to: Flouris AD. *Temperature* 2015; 2(3):328–9; <http://dx.doi.org/10.1080/23328940.2015.1058321>;
 Jänig W. *Temperature* 2015; 2(3):330–1; <http://dx.doi.org/10.1080/23328940.2015.1054553>;
 Morrison SF. *Temperature* 2015; 2(3):332–3; <http://dx.doi.org/10.1080/23328940.2015.1050156>;
 Nagashima K. *Temperature* 2015; 2(3):334–5; <http://dx.doi.org/10.1080/23328940.2015.1053597>;
 Ramsay DS, et al. *Temperature* 2015; 2(3):336–7; <http://dx.doi.org/10.1080/23328940.2015.1050157>; and
 Werner J. *Temperature* 2015; 2(3):338; <http://dx.doi.org/10.1080/23328940.2015.1039690>.

Keywords: brain as a code processor, code system, cold in the skin, core temperature regulation, error-correction effector in the brain, heat-seeking behavior, hypothalamic set-point theory, skin temperature regulation, thermostat of skin temperature, thermosensor of skin temperature

Abbreviations: CNS, central nervous system; KO mice, knockout mice; TRPM8 channel, Transient Receptor Potential M8 type channel.

© Shigeo Kobayashi

*Correspondence to: Shigeo Kobayashi;
 Email: skoba@i.kyoto-u.ac.jp

Submitted: 07/01/2015

Revised: 07/11/2015

Accepted: 07/15/2015

<http://dx.doi.org/10.1080/23328940.2015.1075096>

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.

Flouris: “Comparator” model to explain the natural phenomena is questionable under conditions where conflicting commands are received from different areas of the body, or when autonomic and behavioral thermoregulatory responses are pitted against each other.

Reply: These unnatural experiments⁸ are inadequate to judge whether thermoreceptors are “thermostats” or “thermosensors.” Flouris should explain why the “thermosensor” model to explain natural phenomena is not questionable under these unnatural conditions.

Flouris: “Thermostat” models are primarily philosophical.

Reply: The “thermostat” model is based on patch-clamp analyses of temperature-sensitive receptors (e.g., transient receptor potential M8 type channel (TRPM8 channel)) and phase transition of the channel states at threshold temperature as well as on behavioral analyses of TRPM8-knockout (KO) mice. These are standard procedures in neuroscience.^{9,10} Flouris should explain why the “sensor” model is not “philosophical.” Additionally, using the word “philosophy” for such a criticism should be avoided.

Flouris: Convincing evidence (of the “thermostat” model) is yet to be presented by other research group.

Reply: The “sensor” model is attributed to Adrian,¹¹ a Nobel Prize winner in 1932. Because the “sensor” model remains the most basic concept (which is rather prejudiced) in physiology,^{12,13} no other research group has performed studies based on the “thermostat” model. Consequently, the illogical explanation that a code for skin temperature is decoded into “cold sensation” has been employed. Additionally, although only humans can detect temperature with an artificial thermometer based on a code system, the unreasonable explanation that the brains

of animals can detect skin temperature using this code system has been proposed.

Flouris: It is my belief that, eventually, aspects of the “comparator” model as well as the “hypothalamic proportional control” model will be amalgamated together with elements from other prominent theories of endothermic thermoregulation in order to form a unifying – and complete – theory for the functional architecture of endothermic thermoregulation.

Reply: This comment indicates that Flouris believes that a thermoreceptor (e.g., TRPM8 channel) has 2 conflicting roles: (i) as a thermosensor to monitor skin temperature, and (ii) as a thermostat for skin temperature regulation. Such an amalgamation of “thermosensor” and “thermostat” is not productive for thermoregulation studies.

This is my reply to the letter written by Dr. Jänig.² When skin temperature is decreased below a threshold temperature due to low ambient temperature, we feel “cold” and induce “heat-seeking behaviors.” When we reach a new place at a neutral temperature via this behavior, skin temperature soon recovers to a normal level, and “cold” and “heat-seeking behaviors” cease. This indicates the completion of skin temperature regulation. Thermostats that compare whether skin temperatures are below threshold temperatures should be responsible for these threshold responses in “cold” and “heat-seeking behavior.” To explain the basis of “sensation,” Adrian¹¹ has proposed that a sensory receptor is a sensor (i.e., a transducer) that changes an environmental stimulus into the firing rate code sent to the brain, where the code is somehow decoded into “sensation” of the stimulus. In temperature physiology, a temperature receptor in the skin has been said to be a “thermosensor,” as Jänig quotes from the document written by Hensel. If the sensory system truly works similarly to a signal transduction system, the code for the skin temperature should be decoded into

the “skin temperature” by the brain. However, the illogical explanation that the temperature code is decoded into “cold” has been used.^{11,14} These conflicts show that the sensory system for “sensation” is entirely different from the code system with a sensor. I have proposed a new model in which low temperature-sensitive receptors (e.g., TRPM8 channels) in the skin are thermostat molecules that compare whether the skin temperature is below a whole-cell set-point (e.g., 25°C) and generate thermal error-dependent nerve impulses as command signals (not a code). Behavioral analyses of TRPM8-KO mice show that TRPM8 channels are responsible for inducing threshold responses for “cold” and “heat-seeking behaviors” in conscious mice.^{9,10} As stated by Jänig, “thermosensors or not, this is the question.” We conclude that low temperature-sensitive thermoreceptors in the skin are not thermosensors but thermostats that induce threshold responses for “cold” and “heat-seeking behavior” such that skin temperature may recover to a normal level.

This is my reply to the letter written by **Dr. Morrison**.³

Morrison: Thermoregulation without thermoregulator.

Reply: Since 1986,⁷ I have questioned the “hypothalamic thermostat circuits,” including “set-point theory,” which function based on a thermal code sent from thermoreceptors. Recently, Morrison has reached a similar conclusion that “hypothalamic thermostat circuits” are absent.^{15,16} Nevertheless, he criticizes my article,⁷ which explains that “hypothalamic thermostat circuits” are unlikely (**Fig. 1B**). My article⁷ states that TRPM8 channels in the skin nerve endings are thermostat molecules that compare whether skin temperature is lower than its threshold temperature and generate error-dependent nerve impulses as command signals (not a code). This model is entirely different from the “hypothalamic thermostat circuits” that work based on a code. Behavioral analyses of TRPM8-KO mice show that low temperature-sensitive TRPM8 channels are responsible for inducing “cold” and “heat-seeking behavior” for skin temperature

regulation in mice.^{9,10} Surprisingly, Morrison states that “central thermoregulatory control”¹⁵ is performed without a “controller.”¹⁶ This shows that his model is irrelevant to the thermoregulatory system in conscious mammals. In fact, his experiment merely shows afferent neural pathways that are sensitive to low skin temperatures in anesthetized, immobilized rats.¹⁵ His study of anesthetized rats does not allow the analysis of the thermoregulatory system in conscious rats. Therefore, it is unreasonable to conclude that conscious rats do not have a temperature “controller” from the results obtained in anesthetized rats.

Morrison: We do not know how behavioral thermoregulatory responses are elaborated by the central nervous system (CNS).

Reply: I partly agree with this point. It is difficult to clarify behavioral thermoregulatory responses elaborated by the CNS. In fact, his study¹⁵ of anesthetized rats is most unhelpful for clarifying the brain mechanism underlying behavioral thermoregulation in conscious rats. At present, the most likely method to create a model for behavioral thermoregulation is to use TRPM8-KO mice. Behavioral analyses of conscious TRPM8-KO mice indicate neural connections from skin nerve endings with TRPM8 channels (thermostat molecules) to error-correction effectors for “cold” and “heat-seeking behaviors.”^{9,10} This evidence is sufficient to constitute a model of a thermoregulatory feedback-loop circuit (**Fig. 4**) for behavioral regulation of skin temperatures.⁷ The neural connection is the primary path for the behavioral regulation of skin temperature. Morrison’s model stating that the afferent thermosensitive path is used for a “feedforward control” in core temperature regulation¹⁵ is only his guess and is irrelevant to the results obtained from his experiments with anesthetized rats.

Morrison: The brain is sometimes compared to a computer.

Reply: To explain the basis of sensation, Adrian¹¹ has proposed that the sensory system works similarly to the artificial code system with a sensor. This has

produced the basic theory (which is rather prejudiced) in physiology that the nervous system works similarly to a computer (a processor of a binary code).¹² Since 1986, however, I have questioned the theory that the sensory system is the code system.⁷ Nevertheless, Morrison criticizes my article⁷ as if I state that the brain works similarly to a computer consisting of a “transistor.”

Morrison: An unaddressed question is how (and why) mammalian brain temperature is maintained at the value of ~37°C.

Reply: My article⁷ states the basis of the behavioral regulation of skin temperature. However, as Morrison states, the mechanism employed to maintain core temperature at a nearly constant level in mammals is unknown, although temperature physiologists have studied this for several decades. The “hypothalamic thermostat circuits,” including set-point theory, which function based on a temperature code are unlikely and should be abandoned explicitly for future studies.

Lastly, I ask Morrison to answer a simple question. Are thermoreceptors (e.g., TRPM8 channels) in skin nerve endings sensors for monitoring skin temperature or thermostats⁷ for skin temperature regulation?

This is my reply to the letter written by **Dr. Nagashima**.⁴ The comments made by Nagashima⁴ are similar to those made by Flouris.¹ My article⁷ states the basic mechanism underlying thermoregulation, in which thermoreceptors are “thermostat molecules” for thermoregulation, not “thermosensors” for monitoring temperature.¹¹ Thermoregulation during exercise is important but inadequate to judge whether thermoreceptors are “thermostats” or “thermosensors.”

Nagashima: Does behavioral thermoregulation directly maintain skin temperature?

Reply: This question is difficult to answer. Behavioral analysis of TRPM8-KO mice shows that there are neural connections from nerve endings with TRPM8 channels (thermostat molecules) to cerebral error-correction effectors for inducing

“cold” and “heat-seeking behaviors.” The neural connections are primary pathways for “skin temperature regulation.” Morrison’s view¹⁵ that the afferent thermosensitive neural path is for a “feedforward control” for “core temperature regulation” is irrelevant to the results obtained from his experiments with anesthetized, immobilized rats.

Nagashima: Skin temperature varies among surface regions.

Reply: This fact is inadequate to judge whether thermoreceptors are “thermosensors” or “thermostats.” Nagashima should explain why the “thermosensor” model is appropriate for explaining this fact.

Nagashima: Do thermosensitive molecules act as thermostats?

Reply: I do not understand this question.

Nagashima: Does sensing cold activate behavioral thermoregulation?

Reply: It is difficult to distinguish between “cold sensation” and “thermal discomfort” in mouse studies. In fact, behavioral analysis of TRPM8-KO mice shows that low temperature-sensitive TRPM8 channels are responsible for inducing “cold sensation” and “heat-seeking behaviors.”⁹

This is my reply to the letter written by **Dr. Ramsay et al.**⁵ Ramsay and colleagues precisely understand the significance of my article,⁷ stating that temperature receptors (e.g., TRPM8 channels) in the skin are “thermostats” for skin temperature regulation but not “thermosensors” for thermometry. I agree with their comments that it is important to study thermoregulation under abnormal conditions. I expect that their analyses will be performed based on the “thermostat” model, not on the “thermosensor” model.

This is my reply to the letter written by **Dr. Werner.**⁶ I refute 2 statements by Werner.

Werner: A phenomenon observed on the basic molecular level is not a relevant information parameter on a neuronal circuit or system level.

Reply: This comment is refuted by recent analyses of thermoregulatory behaviors in TRPM8-knockout (KO) mice. Low temperature-induced heat-seeking behavior in TRPM8-KO mice is decreased compared with wild-type mice. This demonstrates that TRPM8 channels are responsible for mediating low temperature-induced “cold” and “heat-seeking behaviors.”^{9,10}

Werner: Temperature receptors in cutaneous nerve endings are not thermostat molecules.

Reply: When skin temperature falls below a threshold temperature due to low ambient temperature, we feel “cold” and induce “heat-seeking behaviors.” When we reach a new place at a neutral temperature, skin temperature soon recovers to a normal level, and “cold” and “heat-seeking behavior” cease (the completion of skin temperature regulation). Thermostats that compare whether skin temperatures are below threshold temperatures should be responsible for the threshold responses for “cold” and “heat-seeking behavior.” My article⁷ states that low temperature-sensitive receptors (such as TRPM8 channels) in the skin are activated to induce nerve impulses when skin temperature falls below a threshold temperature (e.g., 25°C). TRPM8-KO studies show that TRPM8 channels are responsible for inducing “cold” and “heat-seeking behaviors,” as stated above. Thus, we conclude that thermoreceptors in skin nerve endings are thermostat molecules that perform behavioral thermoregulation

for skin temperature regulation.¹⁰ Werner explains that thermoregulation is performed without thermoregulators (i.e., thermostats).¹⁶ However, thermoregulation without thermoregulators is only his guess and unlikely.

Lastly, I ask Werner to answer a simple question. Are these thermoreceptors (e.g., TRPM8 channels) in skin nerve endings sensors for monitoring skin temperature or thermostats⁷ for skin temperature regulation?

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Flouris AD. *Temperature* 2015; 2(3):328-9; <http://dx.doi.org/10.4161/23328940.2014.989793>
2. Jänig W. *Temperature* 2015; 2(3):330-1; <http://dx.doi.org/10.1080/23328940.2015.1054553>
3. Morrison SF. *Temperature* 2015; 2(3):332-3; <http://dx.doi.org/10.1080/23328940.2015.1050156>
4. Nagashima K. *Temperature* 2015; 2(3):334-5; <http://dx.doi.org/10.1080/23328940.2015.1053597>
5. Ramsay DS, et al. *Temperature* 2015; 2(3):336-7; <http://dx.doi.org/10.1080/23328940.2015.1050157>
6. Werner J. *Temperature* 2015; 2(3):338; <http://dx.doi.org/10.1080/23328940.2015.1039690>
7. Kobayashi S. *Temperature* 2015; 2(3):349-54; <http://dx.doi.org/10.1080/23328940.2015.1039190>
8. Ramsay DS, et al. *Temperature* 2014; 1:257-67; PMID:25938127; <http://dx.doi.org/10.4161/23328940.2014.944809>
9. Bautista DM, et al. *Nature* 2007; 448:204-8; PMID:17538622; <http://dx.doi.org/10.1038/nature05910>
10. Tajino K, et al. *PLoS One* 2011; 6:e17504; PMID:21407809; <http://dx.doi.org/10.1371/journal.pone.0017504>
11. Adrian ED. *The Basis of Sensation: The action of the Sense Organs*. London: Christophers; 1928.
12. Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of neural science*. New York: McGraw-Hill; 2000.
13. Hensel H. *Physiol Rev* 1973; 53:948-1017; PMID:4355518
14. Patapoutian A, et al. *Nat Rev Neurosci* 2003; 4:529-39; PMID:12838328; <http://dx.doi.org/10.1038/nrn1141>
15. Nakamura K, et al. *Nat Neurosci* 2008; 11:62-71; PMID:18084288; <http://dx.doi.org/10.1038/nn2027>
16. Romanovsky AA. *Acta Physiol* 2014; 210:498-507; PMID:24716231; <http://dx.doi.org/10.1111/apha.12231>